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EXAMINER	
KIM, YOUNG J	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 01/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/950,024	ZHU ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) *46 and 47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-45* is/are rejected.

7)☒ Claim(s) *4,11 and 13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence Compliance Notice.*

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I, claims 1-45 and the recited combination of nucleotide sequences in the Response received on October 22, 2003 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 46 and 47 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the Response received on October 22, 2003.

Priority

Applicants' preliminary amendment filed on September 12, 2001, amending the first line of the specification to contain reference to an earlier filed non-provisional application, U.S. Serial No. 09/377,907, is acknowledged.

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

According to the Oath and Declaration, it appears that Applicants are desiring to claim benefit to a provisional application 60/097,708 under 35 U.S.C. 119(e). Applicants are advised to amend the first line of the specification to contain a reference to said application.

Appropriate correction is required.

Information Disclosure Statement

The IDS received on September 12, 2001 is acknowledged. A signed copy of its corresponding PTO-1449 is attached hereto.

Drawings

The replacement drawings received on November 7, 2001 are acceptable.

Specification

The specification is objected to because on page 3, beginning at line 13, it makes reference to Figures 4A and 4B. However, the replacement drawings received on November 7, 2001 only comprises Figures 1-3. Applicants' statement submitted with the replacement drawings also indicates that only Figures 1-3 were submitted.

Appropriate correction is required.

Sequence Rules

This application contains sequence disclosures that are encompassed by the definition for nucleotide and/or amino acid sequences set for in 37 CFR 1.82(a)(1) and (a)(2). However, this application fails to comply with the requirement of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications

Containing Nucleotides Sequences And/Or Amino Acid Sequence Disclosures. For example, on page 38, beginning at line 10, there appears a nucleic acid sequence comprising more than 10 nucleotide bases without a SEQ ID Number.

A fully responsive communication will fulfill the sequence rules.

Since the non-compliance is immaterial to search and examination, the application has been acted on with supervisory approval.

Claim Objections

Claim 4 is objected to for being drawn to a non-elected invention. Applicants have elected a specific combination of genes for examination in response to the restriction requirement. However, claim 4 is drawn to any combination of genes selected from Table 1.

Claims 11 and 13 are objected to because of the following informalities: Claim 11 contains two periods. Claim 13 appears to contain a typographical error. Specifically, the phrase, "which the step of determining ***us*** performed using serial analysis of gene expression" appears to contain a typographical error.

Appropriate corrections are required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, and 4-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and its dependent claims 4-44 recite the claim limitation, "wherein the expression levels of the one or more genes correlates with stage of disease progression of HCMV infection." However, its dependent claim 44 also recites the same phrase as ***a further step***:

"The method of claim 1 further comprising the step of: correlating the expression levels of one or more genes with stage of disease progression of the HCMV infection."

Therefore, it becomes ambiguous as to whether the limitation recited in claim 1 is a step that is actively required.

While minor details are not required in method/process claims, at least the basic steps must be recited in a *positive, active fashion*. See *Ex parte Elrich*, 3 USPQ2d, p. 1011 (Bd. Pat App. Int. 1986).

If Applicants would argue that the above limitation in claim 1 is an actively required step, then it becomes indefinite what claim 44 is meant by the phrase, "[t]he method of claim 1 further comprising the step of..." because the recited step is identical to the step in claim 1.

Claim 2 and its dependent claims 4-45 recite the limitation, "wherein the expression levels of the one or more genes correlates with extent of tissue damage caused by HCMV infection." However, its dependent claim 45 also recites the same phrase as ***a further step***:

"The method of claim 2 further comprising the step of: correlating the expression levels of the one or more genes with the extent of tissue damage caused by the HCMV infection."

Therefore, it becomes ambiguous as to whether the limitation recited in claim 2 is a step that is actively required.

While minor details are not required in method/process claims, at least the basic steps must be recited in a *positive, active fashion*. See *Ex parte Elrich*, 3 USPQ2d, p. 1011 (Bd. Pat App. Int. 1986).

If Applicants would argue that the above limitation in claim 2 is an actively required step, then it becomes indefinite what claim 45 is meant by the phrase, "[t]he method of claim 2 *further comprising* the step of..." because the recited step is identical to the step in claim 2.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 15, 24-27, 37, and 44 are rejected under 35 U.S.C. 102(a) as being anticipated by Zhu et al. (PNAS, December 1997, vol. 94, pages 13985-13990).

Claim 1 is drawn to a method of determining the stage of disease caused by HCMV (human cytomegalovirus) infection in a first human sample by determining the expression level of one or more genes which are induced or repressed by HCMV, wherein the expression level of the one or more genes correlates with stage of disease progression of the HCMV infection.

Zhu et al. disclose a method which determines the expression level of 26 different mRNAs (or expression levels of one or more gene) after a human sample is infected with HCMV strain AD169 (Abstract; page 13985, 2nd column, 2nd paragraph). The altered expression level of the mRNAs in the infected human sample is analyzed after 8 hours of infection.

Such assay would inherently determine the early onset of the disease produced by HCMV infection as the claimed method and the disclosed methods accomplish the same determination step, rendering in the anticipation of instant claims 1 and 44.

Table 1 of Zhu et al., on page 13987, discloses a list of genes which are differentially expressed by the host when infected with HCMV, wherein the listed genes are Interferon-stimulated gene 54K, KIAA0062, glyceraldehyde-3-phosphate dehydrogenase, guanylate binding protein I, Mn-superoxide dismutase, microtubular aggregate protein, IFP53, 2'-5' oligoadenylate synthetase, guanylate binding protein II, AF026971, AF026942, AF026943, AF026944, AF026939, and AF026945.

The method by Zhu et al. employs total RNA isolation of human sample to make corresponding cDNA strands. By definition, total RNA contains mRNA, anticipating instant claim 15.

Table 1 of Zhu et al., on page 13987, discloses 15 different genes which are induced or repressed by HCMV infection, thereby anticipating instant claims 24-27.

The human cell sample employed by Zhu et al. comprises human fibroblasts (Abstract), anticipating instant claim 37.

Therefore, the invention as claimed is anticipated by Zhu et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 5-10, 12-14, 16, 28-36, 42, and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhu et al. (PNAS, December 1997, vol. 94, pages 13985-13990) in view of Schena et al. (PNAS, October 1996, vol. 93, pages 10614-10619).

Preliminarily, claim 1 has been rejected under 35 U.S.C. 102. However, claim 1 is included in the present 103 rejection for the sole purpose of delineating the rejection.

Zhu et al. disclose a method which determines the expression level of 26 different mRNAs (or expression levels of one or more gene) after a human sample is infected with HCMV strain AD169 (Abstract; page 13985, 2nd column, 2nd paragraph). The altered expression level of the mRNAs in the infected human sample is analyzed after 8 hours of infection.

Such assay would inherently determine the early onset of the disease produced by HCMV infection as the claimed method and the disclosed methods accomplish the same determination step.

Table 1 of Zhu et al., on page 13987, discloses a list of genes which are differentially expressed by the host when infected with HCMV, wherein the listed genes are Interferon-

stimulated gene 54K, KIAA0062, glyceraldehyde-3-phosphate dehydrogenase, guanylate binding protein I, Mn-superoxide dismutase, microtubular aggregate protein, IFP53, 2'-5' oligoadenylate synthetase, guanylate binding protein II, AF026971, AF026942, AF026943, AF026944, AF026939, and AF026945.

While Zhu et al. disclose that the genes listed in Table 1 are differentially expressed by the host when infected with HCMV, the disclosure is silent on how much the genes are differentially expressed (*i.e.,* folds of expression), as recited in instant claims 5-9.

The method of Zhu et al. does not measure the amount of mRNA expressed by one or more genes (instant claim 10).

The method of Zhu et al. does not employ an array of oligonucleotides (instant claim 12).

The method of Zhu et al. does not employ serial analysis of gene expression (instant claim 13).

The method of Zhu et al. does not employ hybridization of nucleic acids on a solid support (instant claim 14).

The method of Zhu et al. does not employ fluorescent labels (instant claim 16).

The method of Zhu et al. does not employ the expression levels of at least 20 (instant claim 28), 25 (instant claim 29), 30 (instant claim 30), 50 (instant claim 31), 100 (instant claim 32), 200 (instant claim 33), 250 (instant claim 34), 500 (instant claim 35), or 1000 genes (instant claim 36).

The method of Zhu et al. does not compare the expression of the one or more genes from a second human cell sample comprising uninfected cells of the same cell type (instant claim 42).

The method of Zhu et al. does not compare the expression of the one or more genes from a second reference cell sample comprising uninfected cells of the same cell type (instant claim 43).

Schena et al. disclose a human genome microarray which comprises 1000 genes (instant claims 28-36) for the method of monitoring their expression pattern (Abstract; page 10615).

Schena et al. disclose a method of using the microarray to determine the expression fold-difference between the genes immobilized on the microarray (instant claims 12 and 14). Various ranges of fold differences are disclosed (instant claims 5-10) (at page 10618, 2nd column).

Schena et al. disclose a method of using the microarray which fluorescently labels (instant claim 16) the cDNA reverse transcribed from the total mRNA (page 10615, 1st and 2nd columns). The array results are also confirmed via mRNA blotting (pages 10616-10617, 1st column; Table 2; instant claim 10).

Schena et al. disclose a method of using the microarray which measures expression patterns from a T Jurkat cell sample treated with heat and a control T Jurkat cell sample (instant claims 42 and 43).

It would have been *prima facie obvious* to one of ordinary skill in the art at the time the invention was made to employ the microarray of Schena et al. for conducting the differential display analysis of Zhu et al. for the following reasons.

The advantage offered by microarray technology is well known in the art as disclosed by Schena et al.:

"Microarray offers a number of advantages over other potential high-capacity approaches to expression analysis. The chip-based approach enables *small hybridization volumes,*

high array densities, and the use of fluorescence labeling and detection schemes. These features provide a set of performance specifications that are *unattainable* with filter-based approaches...The parallel format of the assay provides *a simultaneous differential expression readout for >1000 genes*...Microarrays of thousands of ESTs will provide a powerful analytical tool for future human gene expression studies" (beginning at page 10618 2nd column to page 10619).

The aspects which were not taught by Zhu et al. - how much the genes are differentially expressed (*i.e.,* folds of expression) (instant claims 5-9); measure of the amount of mRNA expressed by one or more genes (instant claim 10); employment of an array of oligonucleotides (instant claim 12); employment of serial analysis of gene expression (instant claim 13); employment of hybridization of nucleic acids on a solid support (instant claim 14); employment of fluorescent labels (instant claim 16); employment of the expression levels of at least 20 (instant claim 28), 25 (instant claim 29), 30 (instant claim 30), 50 (instant claim 31), 100 (instant claim 32), 200 (instant claim 33), 250 (instant claim 34), 500 (instant claim 35), or 1000 genes (instant claim 36); comparison of the expression of the one or more genes from a second human cell sample comprising uninfected cells of the same cell type (instant claim 42); comparison of the expression of the one or more genes from a second reference cell sample comprising uninfected cells of the same cell type (instant claim 43) – are method steps which are necessarily required when conducing a differential gene expression analysis between a test and a control sample and common to one of ordinary skill in the art in the microarray discipline (as evidenced by Schena et al.). The instant specification also concedes this point:

"One preferred quantifying method is to use confocal microscope and fluorescent labels. The GeneChip® system (Affymetrix, Santa Clara, CA) is particularly suitable for quantifying the hybridization..." (at page 14, lines 14-16).

HCMV is a herpes-like virus wherein its infection is detrimental to human health, correlated with undesirable effects, such as causing complications in unborn fetuses and in people who have weakened immune response (such as AIDS patients). Since Zhu et al. disclose a method of conducting a differential analysis gene expression in a human sample infected with HCMV, one of ordinary skill in the art, at the time the invention was made would have been motivated to employ the microarray of greater than 1000 genes for the advantage of utilizing small hybridization volumes, high array densities, and the use of fluorescence labeling and detection schemes as well as the parallel format of the assay providing a simultaneous differential expression readout for greater than 1000 genes (Schena et al., beginning at page 10618 2nd column to page 10619) with a reasonable expectation of success.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Claims 38-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhu et al. (PNAS, December 1997, vol. 94, pages 13985-13990) in view of Schena et al. (PNAS, October 1996, vol. 93, pages 10614-10619) as applied to claims 1, 5-10, 12-14, 16, 28-36, 42, and 43 above, and further in view of Hock et al. (U.S. Patent No. 5,273,876, December 28, 1993), Vinayagamoorthy et al. (U.S. Patent No. 5,989,873, issued November 23, 1999, filed September 11, 1997, priority September 24, 1996), and Cinque et al. (Intervirology, 1997, vol. 40, no. 2-3, page 85-97).

Zhu et al. and Schena et al. do not disclose that the human samples are lymphocytes, epithelial cells, lung epithelial cells, or neuronal cells.

Hock et al. disclose the presence of HCMV in human lymphocyte sample (column 9, lines 15; instant claim 38).

Vinayagamoorthy et al. disclose the presence of HCMV in human lung samples (column 9, lines 55-65; instant claims 39 and 40).

Cinque et al. disclose the presence of HCMV in neuronal cells (Abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the samples from different human cell types in conducting the method of Zhu et al. and Schena et al. for the following reasons.

The motivation to expand the method of Zhu et al. and Schena et al. to different human cell types is self-evident. Since Hock et al., Vinayagamoorthy et al., and Cinque et al. disclose the presence of HCMV in different human cell types, one of ordinary skill in the art, at the time the invention was made, would have been motivated to extend the method of Zhu et al. and Schena et al. to also investigate for the presence of HCMV in different human cell types. Since RNA isolation from a cell sample is a well established and known technique, one of ordinary skill in the art, at the time the invention was made would have had a reasonable expectation of success in extending the method of Zhu et al. and Schena et al. to include the different cell types disclosed by Hock et al., Vinayagamoorthy et al., and Cinque et al.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Claims 2 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhu et al. (PNAS, December 1997, vol. 94, pages 13985-13990) in view of Soderberg-Naucler et al. (Herpes, 1997, vol. 4, no. 1, pages 4-9).

Zhu et al. disclose a method which determines the expression level of 26 different mRNAs (or expression levels of one or more gene) after a human sample is infected with HCMV strain AD169 (Abstract; page 13985, 2nd column, 2nd paragraph). The altered expression level of the mRNAs in the infected human sample is analyzed after 8 hours of infection.

Table 1 of Zhu et al., on page 13987, discloses a list of genes which are differentially expressed by the host when infected with HCMV, wherein the listed genes are Interferon-stimulated gene 54K, KIAA0062, glyceraldehyde-3-phosphate dehydrogenase, guanylate binding protein I, Mn-superoxide dismutase, microtubular aggregate protein, IFP53, 2'-5' oligoadenylate synthetase, guanylate binding protein II, AF026971, AF026942, AF026943, AF026944, AF026939, and AF026945.

The method by Zhu et al. employs total RNA isolation of human sample to make corresponding cDNA strands. By definition, total RNA contains mRNA.

Table 1 of Zhu et al., on page 13987, discloses 15 different genes which are induced or repressed by HCMV infection.

The human cell sample employed by Zhu et al. comprises human fibroblasts (Abstract).

While Zhu et al. conduct the method of determining differential gene expression analysis in a human sample infected with HCMV, the artisans do not explicitly state that a tissue damage correlation can be made (instant claims 2 and 45).

Soderberg-Naucler et al. disclose that HCMV is correlated with causing tissue damage in human patients (Abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to correlate the tissue damage from the results of the differential gene expression analysis method of Zhu et al. for the following reasons.

Although Zhu et al. do not explicitly disclose that tissue damage correlation can be made, it is an art-recognized fact, as evidenced by Soderberg-Naucler et al., that a virus replicates in its host and when allowed to proliferate, results in tissue damage. Since the method of Zhu et al. discloses a method of determining the state of infection in a patient infected with HCMV, one of ordinary skill in the art, at the time the invention was made would have had a reasonable expectation of success in correlating that some tissue damage would have occurred as a result of the infection. In *In re Preda*, 401 F.2d 825, 826, 159 USPQ 342 (CCPA 1968), the court expressed that, "in considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inference which one skilled in the art would reasonably be expected to draw therefrom."

Therefore, the invention as claimed is obvious over the cited references.

Claims 5-10, 12-16, 24-37, and 42-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhu et al. (PNAS, December 1997, vol. 94, pages 13985-13990) in view of Soderberg-Naucler et al. (Herpes, 1997, vol. 4, no. 1, pages 4-9) as applied to claims 2 and 45 above, and further in view of Schena et al. (PNAS, October 1996, vol. 93, pages 10614-10619).

In addition to the teachings discussed above, the method by Zhu et al. employs total RNA isolation of human sample to make corresponding cDNA strands. By definition, total RNA contains mRNA (instant claim 15).

Table 1 of Zhu et al., on page 13987, discloses 15 different genes which are induced or repressed by HCMV infection (instant claims 24-27).

The human cell sample employed by Zhu et al. comprises human fibroblasts (Abstract; instant claim 37).

While Zhu et al. disclose that the genes listed in Table 1 are differentially expressed by the host when infected with HCMV, Zhu et al. and Soderberg-Naucler et al. are silent on how much the genes are differentially expressed (*i.e.,* folds of expression), as recited in instant claims 5-9.

The teachings of Zhu et al. and Soderberg-Naucler et al. do not measure the amount of mRNA expressed by one or more genes (instant claim 10).

The teachings of Zhu et al. and Soderberg-Naucler et al. do not employ an array of oligonucleotides (instant claim 12).

The teachings of Zhu et al. and Soderberg-Naucler et al. do not employ serial analysis of gene expression (instant claim 13).

The teachings of Zhu et al. and Soderberg-Naucler et al. do not employ hybridization of nucleic acids on a solid support (instant claim 14).

The teachings of Zhu et al. and Soderberg-Naucler et al. do not employ fluorescent labels (instant claim 16).

The teachings of Zhu et al. and Soderberg-Naucler et al. do not employ the expression levels of at least 20 (instant claim 28), 25 (instant claim 29), 30 (instant claim 30), 50 (instant claim 31), 100 (instant claim 32), 200 (instant claim 33), 250 (instant claim 34), 500 (instant claim 35), or 1000 genes (instant claim 36).

The teachings of Zhu et al. and Soderberg-Naucler et al.do not compare the expression of the one or more genes from a second human cell sample comprising uninfected cells of the same cell type (instant claim 42).

The teachings of Zhu et al. and Soderberg-Naucler et al. do not compare the expression of the one or more genes from a second reference cell sample comprising uninfected cells of the same cell type (instant claim 43).

Schena et al. disclose a human genome microarray which comprises 1000 genes (instant claims 28-36) for the method of monitoring their expression pattern (Abstract; page 10615).

Schena et al. disclose a method of using the microarray to determine the expression fold-difference between the genes immobilized on the microarray (instant claims 12 and 14). Various ranges of fold differences are disclosed (instant claims 5-10) (at page 10618, 2nd column).

Schena et al. disclose a method of using the microarray which fluorescently labels (instant claim 16) the cDNA reverse transcribed from the total mRNA (page 10615, 1st and 2nd columns). The array results are also confirmed via mRNA blotting (pages 10616-10617, 1st column; Table 2; instant claim 10).

Schena et al. disclose a method of using the microarray which measures expression patterns from a T Jurkat cell sample treated with heat and a control T Jurkat cell sample (instant claims 42 and 43).

It would have been *prima facie obvious* to one of ordinary skill in the art at the time the invention was made to employ the microarray of Schena et al. for correlating the extent of tissue damage in a sample via differential display analysis of Zhu et al. and Soderberg-Naucler et al. for the following reasons.

The advantage offered by microarray technology is well known in the art as disclosed by Schena et al.:

> "Microarray offers a number of advantages over other potential high-capacity approaches to expression analysis. The chip-based approach enables *small hybridization volumes, high array densities, and the use of fluorescence labeling and detection schemes*. These features provide a set of performance specifications that are *unattainable* with filter-based approaches...The parallel format of the assay provides *a simultaneous differential expression readout for >1000 genes*...Microarrays of thousands of ESTs will provide a powerful analytical tool for future human gene expression studies" (beginning at page 10618 2nd column to page 10619).

The aspects which were not taught by Zhu et al. - how much the genes are differentially expressed (*i.e.,* folds of expression) (instant claims 5-9); measure of the amount of mRNA expressed by one or more genes (instant claim 10); employment of an array of oligonucleotides (instant claim 12); employment of serial analysis of gene expression (instant claim 13); employment of hybridization of nucleic acids on a solid support (instant claim 14); employment of fluorescent labels (instant claim 16); employment of the expression levels of at least 20 (instant claim 28), 25 (instant claim 29), 30 (instant claim 30), 50 (instant claim 31), 100 (instant

claim 32), 200 (instant claim 33), 250 (instant claim 34), 500 (instant claim 35), or 1000 genes (instant claim 36); comparison of the expression of the one or more genes from a second human cell sample comprising uninfected cells of the same cell type (instant claim 42); comparison of the expression of the one or more genes from a second reference cell sample comprising uninfected cells of the same cell type (instant claim 43) – are method steps which are necessarily required when conducing a differential gene expression analysis between a test and a control sample and common to one of ordinary skill in the art in the microarray discipline (as evidenced by Schena et al.). The instant specification also concedes this point:

> "One preferred quantifying method is to use confocal microscope and fluorescent labels. The GeneChip® system (Affymetrix, Santa Clara, CA) is particularly suitable for quantifying the hybridization..." (at page 14, lines 14-16).

HCMV is a herpes-like virus wherein its infection is detrimental to human health, correlated with undesirable effects, such as causing complications in unborn fetuses and in people who have weakened immune response (such as AIDS patients). Since Zhu et al. disclose a method of conducting a differential analysis gene expression in a human sample infected with HCMV, one of ordinary skill in the art, at the time the invention was made would have been motivated to employ the microarray of greater than 1000 genes for the advantage of utilizing small hybridization volumes, high array densities, and the use of fluorescence labeling and detection schemes as well as the parallel format of the assay providing a simultaneous differential expression readout for greater than 1000 genes (Schena et al., beginning at page 10618 2nd column to page 10619) with a reasonable expectation of success. Finally, the results obtained by combining the teachings of Zhu et al. and Schena et al. would have allowed the

ordinarily skilled artisans, at the time the invention was made, to correlate the extent of tissue damage caused by the HCMV infection as already set forth above.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Claims 38-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhu et al. (PNAS, December 1997, vol. 94, pages 13985-13990) in view of Soderberg-Naucler et al. (Herpes, 1997, vol. 4, no. 1, pages 4-9) as applied to claims 2 and 45 above, and further in view of Hock et al. (U.S. Patent No. 5,273,876, December 28, 1993), Vinayagamoorthy et al. (U.S. Patent No. 5,989,873, issued November 23, 1999, filed September 11, 1997, priority September 24, 1996), and Cinque et al. (Intervirology, 1997, vol. 40, no. 2-3, page 85-97).

Zhu et al. and Soderberg-Naucler et al. do not disclose that the human samples are lymphocytes, epithelial cells, lung epithelial cells, or neuronal cells.

Hock et al. disclose the presence of HCMV in human lymphocyte sample (column 9, lines 15; instant claim 38).

Vinayagamoorthy et al. disclose the presence of HCMV in human lung samples (column 9, lines 55-65; instant claims 39 and 40).

Cinque et al. disclose the presence of HCMV in neuronal cells (Abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the samples from different human cell types in conducting the method of Zhu et al. and Soderberg-Naucler et al. for the following reasons.

The motivation to expand the method of Zhu et al. and Soderberg-Naucler et al. to different human cell types is self-evident. Since Hock et al., Vinayagamoorthy et al., and Cinque

et al. disclose the presence of HCMV in different human cell types, one of ordinary skill in the art, at the time the invention was made, would have been motivated to extend the method of Zhu et al. and Soderberg-Naucler et al. to also investigate for the presence of HMCV in different human cell types. Since RNA isolation from a cell sample is a well established and known technique, one of ordinary skill in the art, at the time the invention was made would have had a reasonable expectation of success in extending the method of Zhu et al. and Soderberg-Naucler et al. to include the different cell types disclosed by Hock et al., Vinayagamoorthy et al., and Cinque et al.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Claim 3, 5-16, 24-37, and 42-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhu et al. (PNAS, December 1997, vol. 94, pages 13985-13990) in view of Schena et al. (PNAS, October 1996, vol. 93, pages 10614-10619), Cocks et al. (U.S. Patent No. 6,607,879 B1, issued August 19, 2003, filed February 9, 1998), and Huey et al. (American Journal of Physiology-Cell Physiology, 1996, vol. 271, no. 6, pages C2016-C2026).

Zhu et al. disclose a method which determines the expression level of 26 different mRNAs (or expression levels of one or more gene) after a human sample is infected with HCMV strain AD169 (Abstract; page 13985, 2nd column, 2nd paragraph). The altered expression level of the mRNAs in the infected human sample is analyzed after 8 hours of infection.

Table 1 of Zhu et al., on page 13987, discloses a list of genes which are differentially expressed by the host when infected with HCMV, wherein the listed genes are Interferon-stimulated gene 54K, KIAA0062, glyceraldehyde-3-phosphate dehydrogenase, guanylate

binding protein I, Mn-superoxide dismutase, microtubular aggregate protein, IFP53, 2'-5' oligoadenylate synthetase, guanylate binding protein II, AF026971, AF026942, AF026943, AF026944, AF026939, and AF026945.

The method by Zhu et al. employs total RNA isolation of human sample to make corresponding cDNA strands. By definition, total RNA contains mRNA (instant claim 15).

Table 1 of Zhu et al., on page 13987, discloses 15 different genes which are induced or repressed by HCMV infection (instant claims 24-27).

The human cell sample employed by Zhu et al. comprises human fibroblasts (Abstract; instant claim 37).

Zhu et al. do not teach a method of screening for a candidate drug for preventing disease symptoms caused by HCMV (instant claim 3).

While Zhu et al. disclose that the genes listed in Table 1 are differentially expressed by the host when infected with HCMV, the disclosure is silent on how much the genes are differentially expressed (*i.e.,* folds of expression), as recited in instant claims 5-9.

The method of Zhu et al. does not measure the amount of mRNA expressed by one or more genes (instant claim 10).

The method of Zhu et al. does not measure the amount of protein level of the one or more genes (instant claim 11).

The method of Zhu et al. does not employ an array of oligonucleotides (instant claim 12).

The method of Zhu et al. does not employ serial analysis of gene expression (instant claim 13).

The method of Zhu et al. does not employ hybridization of nucleic acids on a solid support (instant claim 14).

The method of Zhu et al. does not employ fluorescent labels (instant claim 16).

The method of Zhu et al. does not employ the expression levels of at least 20 (instant claim 28), 25 (instant claim 29), 30 (instant claim 30), 50 (instant claim 31), 100 (instant claim 32), 200 (instant claim 33), 250 (instant claim 34), 500 (instant claim 35), or 1000 genes (instant claim 36).

The method of Zhu et al. does not compare the expression of the one or more genes from a second human cell sample comprising uninfected cells of the same cell type (instant claim 42).

The method of Zhu et al. does not compare the expression of the one or more genes from a second reference cell sample comprising uninfected cells of the same cell type (instant claim 43).

Schena et al. disclose a human genome microarray which comprises 1000 genes (instant claims 28-36) for the method of monitoring their expression pattern (Abstract; page 10615).

Schena et al. disclose a method of using the microarray to determine the expression fold-difference between the genes immobilized on the microarray (instant claims 12 and 14). Various ranges of fold differences are disclosed (instant claims 5-10) (at page 10618, 2nd column).

Schena et al. disclose a method of using the microarray which fluorescently labels (instant claim 16) the cDNA reverse transcribed from the total mRNA (page 10615, 1st and 2nd columns). The array results are also confirmed via mRNA blotting (pages 10616-10617, 1st column; Table 2; instant claim 10).

Schena et al. disclose a method of using the microarray which measures expression patterns from a T Jurkat cell sample treated with heat and a control T Jurkat cell sample (instant claims 42 and 43).

Cocks et al. disclose a well-known method of using a microarray to screen for candidate drugs (column 15, lines 12-17).

Huey et al. disclose a well known method of measuring mRNA levels and its encoded protein levels in expression assays (Abstract).

It would have been *prima facie obvious* to one of ordinary skill in the art at the time the invention was made to employ the microarray of Schena et al. for conducting the differential display analysis of Zhu et al. for screening candidate drugs for the following reasons.

Initially, the motivation to conduct the differential display analysis of Zhu et al. on a microarray is based on the advantage offered by microarray technology which is well known in the art (Schena et al.):

> "Microarray offers a number of advantages over other potential high-capacity approaches to expression analysis. The chip-based approach enables *small hybridization volumes, high array densities, and the use of fluorescence labeling and detection schemes*. These features provide a set of performance specifications that are *unattainable* with filter-based approaches...The parallel format of the assay provides *a simultaneous differential expression readout for >1000 genes*...Microarrays of thousands of ESTs will provide a powerful analytical tool for future human gene expression studies" (beginning at page 10618 2nd column to page 10619; Schena et al.).

The aspects which were not taught by Zhu et al. - how much the genes are differentially expressed (*i.e.,* folds of expression) (instant claims 5-9); measure of the amount of mRNA expressed by one or more genes (instant claim 10); employment of an array of oligonucleotides (instant claim 12); employment of serial analysis of gene expression (instant claim 13); employment of hybridization of nucleic acids on a solid support (instant claim 14); employment of fluorescent labels (instant claim 16); employment of the expression levels of at least 20 (instant claim 28), 25 (instant claim 29), 30 (instant claim 30), 50 (instant claim 31), 100 (instant claim 32), 200 (instant claim 33), 250 (instant claim 34), 500 (instant claim 35), or 1000 genes (instant claim 36); comparison of the expression of the one or more genes from a second human cell sample comprising uninfected cells of the same cell type (instant claim 42); comparison of the expression of the one or more genes from a second reference cell sample comprising uninfected cells of the same cell type (instant claim 43) – are method steps which are necessarily required when conducing a differential gene expression analysis between a test and a control sample and common to one of ordinary skill in the art in the microarray discipline (as evidenced by Schena et al.). The instant specification also concedes this point:

> "One preferred quantifying method is to use confocal microscope and fluorescent labels. The GeneChip® system (Affymetrix, Santa Clara, CA) is particularly suitable for quantifying the hybridization..." (at page 14, lines 14-16).

HCMV is a herpes-like virus wherein its infection is detrimental to human health, correlated with undesirable effects, such as causing complications in unborn fetuses and in people who have weakened immune response (such as AIDS patients). Since Zhu et al. disclose a method of conducting a differential analysis gene expression in a human sample infected with

HCMV, one of ordinary skill in the art, at the time the invention was made would have been motivated to employ the microarray of greater than 1000 genes for the advantage of utilizing small hybridization volumes, high array densities, and the use of fluorescence labeling and detection schemes as well as the parallel format of the assay providing a simultaneous differential expression readout for greater than 1000 genes (Schena et al., beginning at page 10618 2nd column to page 10619) with a reasonable expectation of success.

Additionally, the screening of drug candidates via use of microarray expression profiling is also well known in the art, as evidenced by Cocks et al.:

"Also, researchers can use the microarray to rapidly screen large numbers of candidate drugs, looking for ones that an expression profile similar to those of known therapeutic effects." (column 15, lines 12-17).

Therefore, one of ordinary skill in the art, at the time the invention was made, would have been motivated to utilize the advantage of *rapidly screening* large numbers of candidate drugs on a microarray in order to find a candidate drug that prevents symptoms caused by HCMV with a reasonable expectation of success.

With regard to the limitation regarding the detection of the protein level instead of the mRNA level, since it is well-known fact that the level of a protein is correlated with its encoding mRNA level, one of ordinary skill in the art would have recognized that the detection of proteins encoded by the mRNAs detected by Zhu et al. Schena et al., and Cocks et al. would have revealed the same information. This fact is clearly evident in the disclosure of Huey et al. (*ut* supra). Also, the instant specification concedes this fact:

"The method by which expression levels are ***determined is not critical to the invention***. ***Either mRNA or protein expression*** from one or more genes may be determined." (page 12, lines 4-6; Specification).

Therefore, in view of the disclosure of Huey et al., one of ordinary skill in the art, at the time the invention was made would have had a reasonable expectation of success in assaying for the protein expressed by the mRNAs identified by Zhu et al. and Schena et al., and Cocks et al.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Claims 38-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhu et al. (PNAS, December 1997, vol. 94, pages 13985-13990) in view of Schena et al. (PNAS, October 1996, vol. 93, pages 10614-10619) and Cocks et al. (U.S. Patent No. 6,607,879 B1, issued August 19, 2003, filed February 9, 1998) as applied to claims 3, 5-10, 12-16, 24-37, and 42-43 above, and further in view of Hock et al. (U.S. Patent No. 5,273,876, December 28, 1993), Vinayagamoorthy et al. (U.S. Patent No. 5,989,873, issued November 23, 1999, filed September 11, 1997, priority September 24, 1996), and Cinque et al. (Intervirology, 1997, vol. 40, no. 2-3, page 85-97).

Zhu et al. Schena et al., and Cocks et al. do not disclose that the human samples are lymphocytes, epithelial cells, lung epithelial cells, or neuronal cells.

Hock et al. disclose the presence of HCMV in human lymphocyte sample (column 9, lines 15; instant claim 38).

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Cinque et al. disclose the presence of HCMV in neuronal cells (Abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the samples from different human cell types in conducting the method of Zhu et al., Schena et al., and Cocks et al. for the following reasons.

The motivation to expand the method of Zhu et al., Schena et al., and Cocks et al. to different human cell types is self-evident. Since Hock et al., Vinayagamoorthy et al., and Cinque et al. discloses the presence of HCMV in different human cell types, one of ordinary skill in the art, at the time the invention was made, would have been motivated to extend the method of Zhu et al., Schena et al., and Cocks et al. to also investigate for the presence of HCMV in different human cell types. Since RNA isolation from a cell sample is a well established and known technique, one of ordinary skill in the art, at the time the invention was made would have had a reasonable expectation of success in extending the method of Zhu et al., Schena et al., and Cocks et al. to include the different cell types disclosed by Hock et al., Vinayagamoorthy et al., and Cinque et al.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zhu et al. (PNAS, December 1997, vol. 94, pages 13985-13990) in view of Huey et al. (American Journal of Physiology-Cell Physiology, 1996, vol. 271, no. 6, pages C2016-C2026).

Claim 11 is drawn to a method of determining the stage of disease caused by HCMV (human cytomegalovirus) infection in a first human sample by determining the protein expression level of one or more genes which are induced or repressed by HCMV, wherein the protein expression level of the one or more genes correlates with stage of disease progression of the HCMV infection.

Zhu et al. disclose a method which determines the expression level of 26 different mRNAs (or expression levels of one or more gene) after a human sample is infected with HCMV strain AD169 (Abstract; page 13985, 2nd column, 2nd paragraph). The altered expression level of the mRNAs in the infected human sample is analyzed after 8 hours of infection.

Such assay would inherently determine the early onset of the disease produced by HCMV infection as the claimed method and the disclosed methods accomplish the same determination (instant claim 1).

Zhu et al. do not measure the expressed protein level.

Huey et al. disclose a well known method of measuring mRNA levels and its encoded protein levels in expression assays (Abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to measure the level of the protein instead of the levels of the mRNA for the following reasons.

Since the level of mRNA is closely correlated with the protein levels, one of ordinary skill in the art would have recognized that the detection of proteins encoded by the mRNAs detected by Zhu et al. would have revealed the same information. This fact is clearly evident in the disclosure of Huey et al. (*ut* supra). Also, the instant specification concedes this fact:

"The method by which expression levels are ***determined is not critical to the invention***. ***Either mRNA or protein expression*** from one or more genes may be determined." (page 12, lines 4-6; Speicification).

Therefore, in view of the disclosure of Huey et al., one of ordinary skill in the art, at the time the invention was made would have had a reasonable expectation of success in assaying for the protein expressed by the mRNAs identified by Zhu et al.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zhu et al. (PNAS, December 1997, vol. 94, pages 13985-13990) in view of Soderberg-Naucler et al. (Herpes, 1997, vol. 4, no. 1, pages 4-9) as applied to claims 2 and 45 above, and further in view of Huey et al. (American Journal of Physiology-Cell Physiology, 1996, vol. 271, no. 6, pages C2016-C2026).

The method of Zhu et al. and Soderberg-Naucler et al. do not measure the expressed protein level.

Huey et al. disclose a well-known method of measuring mRNA levels and its encoded protein levels in expression assays (Abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to measure the level of the protein instead of the levels of the mRNA for the following reasons.

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This fact is clearly evident in the disclosure of Huey et al. (*ut* supra). Also, the instant specification concedes this fact:

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Therefore, the invention as claimed is *prima facie* obvious over the cited references.

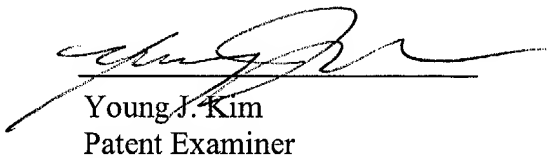
Conclusion

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (703) 308-9348 (**effective January 14, 2004, changed to 571-272-0785**). The Examiner can normally be reached from 8:30 a.m. to 6:00 p.m. Monday through Thursday. If attempts to reach the Examiner by telephone are unsuccessful, the Primary Examiner in charge of the prosecution, Dr. Kenneth Horlick, can be reached at (703)-308-3905 (**effective January 14, 2004, changed to 571-272-0784**). If the attempts to reach the above Examiners are unsuccessful, the Examiner's supervisor, Gary Benzion, can be reached at (703) 308-1119. Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO

DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (703) 872-9306. For Unofficial documents, faxes can be sent directly to the Examiner at (703) 746-3172 (**effective January 14, 2004, changed to 571-273-0785**). Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.



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1/12/04